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PRIMARY EYE IRRITATION POTENTIAL OF INSECT REPELLENTS  
METHYL NN'-DIHEXYLE... (U) LETTERMAN ARMY INST OF  
RESEARCH PRESIDIO OF SAN FRANCISCO CA  
T P KELLNER ET AL. AUG 83 LAIR-154

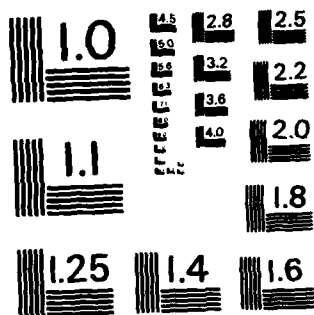
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MICROCOPY RESOLUTION TEST CHART  
NATIONAL BUREAU OF STANDARDS-1963-A

INSTITUTE REPORT NO. 154

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**PRIMARY EYE IRRITATION POTENTIAL OF INSECT REPELLENTS:**

**Methyl N,N'-Dihexylethylenediaminemonocarbamate (CHR4),  
(E)-1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline (CHR5) and  
1,2,3,4-Tetrahydro-6-Methyl-1-(3-Methyl-1-Oxo-2-Butenyl) Quinoline (CHR6)**

**THOMAS P. KELLNER, BA, SP4**

**and**

**MARTHA A. HANES, DVM, CPT VC**

**TOXICOLOGY GROUP,  
DIVISION OF RESEARCH SUPPORT**

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**AUGUST 1983**

**Toxicology Series 56**

**LETTERMAN ARMY INSTITUTE OF RESEARCH  
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129**

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**Primary Eye Irritation Potential of Insect Repellents: Methyl N,N'**  
**Dihexylethylenediaminemonocarbamate (CHR4), (E)-1,2,3,4-Tetrahydro-6-**  
**Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline (CHR5) and 1,2,3,4-**  
**Tetrahydro-6-Methyl-1-(3-Methyl-1-Oxo-2-Butenyl) Quinoline (CHR6)**  
**(Toxicology Series 56)--Kellner and Hanes**

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In conducting the research described in this report, the investigation adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.

This material has been reviewed by Letterman Army Institute of Research and there is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense (AR 360.5)

  
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8 Aug 83

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER LAIR Institute Report No. 154	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Primary Eye Irritation Potential of Insect Repellents: CHR4, CHR5, and CHR6*		5. TYPE OF REPORT & PERIOD COVERED Final 27 Sep - 12 Oct 82
7. AUTHOR(s) Thomas P. Kellner, BA, SP4 Martha A. Hanes, DVM, CPT VC		6. PERFORMING ORG. REPORT NUMBER
9. PERFORMING ORGANIZATION NAME AND ADDRESS Toxicology Group, Division of Research Support Letterman Army Institute of Research Presidio of San Francisco, CA 94129		8. CONTRACT OR GRANT NUMBER(s)
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research and Development Command Fort Detrick Frederick, MD 21701		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS Project 3M19770A871 62
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17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES *CHR4 = Methyl N,N'-Dihexylethylenediaminemonocarbamate *CHR5 = (E)-1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline *CHR6 = 1,2,3,4-Tetrahydro-6-Methyl-1-(3-Methyl-1-Oxo-2-Butenyl) Quinoline		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Eye Irritation Potential, Insect Repellent, Methyl N,N'-Dihexylethylenediamine-monocarbamate, (E)-1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline, 1,2,3,4-Tetrahydro-6-Methyl-1-(3-Methyl-1-Oxo-2-Butenyl) Quinoline		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The insect repellents methyl N,N'-dihexylethylenediaminemonocarbamate (CHR4), (E)-1,2,3,4-tetrahydro-6-methyl-1-(2-methyl-1-oxo-2-butenyl) quinoline (CHR5), and 1,2,3,4-tetrahydro-6-methyl-1-(3-methyl-1-oxo-2-butenyl) quinoline (CHR6) were tested for ocular irritation potential using the Primary Eye Irritation Test on rabbits. The study was conducted in compliance with the Good Laboratory Practice regulations. Of the three repellents tested, only CHR4, 0.1 ml undiluted, applied to the eyes of rabbits resulted in readily noticeable		

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corneal opacity, conjunctival redness, and conjunctival chemosis. CHR5 and CHR6 produced irritation of the conjunctiva early in the study, but the level of severity did not meet the criteria for positive eye irritants.

# ABSTRACT

The insect repellents methyl N,N'-dihexylethylenediamine-monocarbamate (CHR4), (E)-1,2,3,4-tetrahydro-6-methyl-1-(2-methyl-1-oxo-2-butenyl) quinoline (CHR5), and 1,2,3,4-tetrahydro-6-methyl-1-(3-methyl-1-oxo-2-butenyl) quinoline (CHR6) were tested for ocular irritation potential using the Primary Eye Irritation Test on rabbits. The study was conducted in compliance with the Good Laboratory Practice regulations. Of the three repellents tested, only CHR4 was shown to be a positive ocular irritant. CHR4, 0.1 ml undiluted, applied to the eyes of rabbits resulted in readily noticeable corneal opacity, conjunctival redness, and conjunctival chemosis. CHR5 and CHR6 produced irritation of the conjunctiva early in the study, but the level of severity did not meet the criteria for positive eye irritants.

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## PREFACE

TYPE REPORT: Primary Eye Irritation GLP Study Report

TESTING FACILITY: US Army Medical Research and Development Command  
Letterman Army Institute of Research  
Division of Research Support  
Presidio of San Francisco, CA 94129

SPONSOR: US Army Medical Research and Development Command  
Letterman Army Institute of Research  
Presidio of San Francisco, CA 94129

PROJECT/WORK UNIT/APC: Prevention of Military Disease Hazards  
3M19770A871, Work Unit 201, APC FLO7

GLP STUDY NUMBER: 82027

STUDY DIRECTOR: COL John T. Fruin, DVM, PhD, VC, Diplomate of  
American College of Veterinary Preventive Medicine

PRINCIPAL INVESTIGATOR: Martha A. Hanes, DVM, CPT VC

CO-PRINCIPAL INVESTIGATOR: Thomas P. Kellner, SP4, BA

REPORT AND DATA MANAGEMENT: A copy of the final report, study protocols,  
raw data, retired SOPs and an aliquot of each  
test compound will be retained in the LAIR  
Archives.

TEST SUBSTANCES: A. Methyl N, N'-Dihexylethylenediaminemonocarbamate  
(CHR4)

B. (E)-1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-  
Oxo-2-Butenyl) Quinoline (CHR5)

C. 1,2,3,4-Tetrahydro-6-Methyl-1-(3-Methyl-1-  
Oxo-2-Butenyl) Quinoline (CHR6)

INCLUSIVE STUDY DATES: 27 September - 12 October 1982

OBJECTIVE: To evaluate the primary ocular irritation potential of  
insect repellents CHR4, CHR5, and CHR6.

#### ACKNOWLEDGMENT

The authors wish to thank Carolyn M. Lewis, MS, for her assistance during the study.

SIGNATURES OF PRINCIPAL SCIENTISTS AND MANAGERS INVOLVED IN THE STUDY:

We, the undersigned, believe the study number 82027 described in this report to be scientifically sound and the results in this report and interpretation to be valid. The study was conducted to comply, to the best of our ability, with the Good Laboratory Practice Regulations for Medical Laboratory Studies, outlined by the Food and Drug Administration.

John T. Fruin 4 May 83  
JOHN T. FRUIN / DATE  
COL, VC  
Study Director

Thomas P. Kellner 4 May 83  
THOMAS P. KELLNER, BA / DATE  
SP4, USA  
Co-Principal Investigator

Martha A. Hanes 4 May 83  
MARTHA A. HANES / DATE  
CPT, VC  
Principal Investigator



DEPARTMENT OF THE ARMY  
LETTERMAN ARMY INSTITUTE OF RESEARCH  
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

REPLY TO  
ATTENTION OF:

SGRD-ULZ-QA

9 Jun 83

MEMORANDUM FOR RECORD


SUBJECT: Report of GLP Compliance

I hereby certify that in relation to LAIR GLP study 82027 the following inspections were made:

28 Sep 82  
1 Oct 82  
12 Oct 82

The report and raw data for this study were audited on 8 Jun 83.

Routine inspections with no adverse findings are reported quarterly, thus these inspections are also included in the Oct 82 and Jan 83 report to management and the Study Director.

  
NELSON R. POWERS, Ph.D.  
CPT, MSC  
Quality Assurance Officer

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Letterman Army Institute of Research (LAIR) has been directed to participate in the development of better insect repellents for the protection of soldiers from insects and insect-borne diseases in the field. In the last several years, investigators in the Division of Cutaneous Hazards at LAIR have tested a large number of chemical compounds, submitted by SRI-International; the U.S. Department of Agriculture (USDA); and private industry, against a variety of mosquitoes, sand flies, fleas, bugs, ticks, and mites in animal and in in vitro test systems. Several of these materials have shown sufficient repellent activity and persistence on the skin of animals to warrant consideration for use in lieu of, or in conjunction with, the current troop-issue repellent, 71.25% diethyl-toluamide (m-DEET) in ethanol. The investigators have also evaluated a number of new formulations of m-DEET prepared at LAIR or submitted by private industry. Several of these new formulations have been more persistent on the skin in tests on animals than the current troop-issue repellent.

We now plan to test on human volunteers the most promising of the new compounds and formulations to confirm the results that have been obtained in the in vitro and animal tests to evaluate the performance of these agents under conditions of actual use. Before this can be done, it is necessary to obtain certain toxicity data on each compound or formulation to insure that it is safe for application to the skin. The basic toxicity tests required for experimental use of the new compounds and formulations on human volunteers are prescribed by the LAIR and U.S. Army Medical Research and Development Command (USAMRDC) Human Use Committees. If adverse toxicity data are obtained in these tests, the material(s) will be eliminated from consideration, and the prospective tests on human volunteers will not be conducted. The toxicity testing program thereby serves both as a safety factor and a secondary screen in the repellent development scheme.

### Objective of the Study

The objective of the study is to evaluate the primary ocular irritation potential of insect repellents:

**Methyl N,N'-dihexylethylenediaminemonocarbamate (CHR4)**

(E)-1,2,3,4-tetrahydro-6-methyl-1-(2-methyl-1-oxo-2-butenyl) quinoline (CHR5)

1,2,3,4-tetrahydro-6-methyl-1-(3-methyl-1-oxo-2-butenyl)  
quinoline (CHR6)

## METHODS

### Test Substances

1. Chemical name: Methyl-N,N'-Dihexylethylenediamine-Monocarbamate (CHR4)

Chemical Abstract Service Registry No.: None

**Structural formula:**

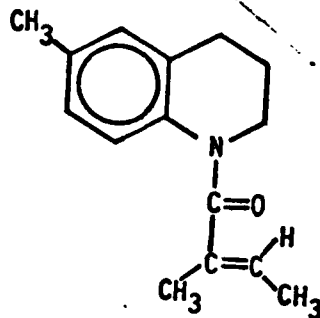
$$\text{CH}_3(\text{CH}_2)_5\text{NH}(\text{CH}_2)_2\underset{\begin{array}{c} | \\ \text{CO}_2\text{CH}_3 \end{array}}{\text{N}}(\text{CH}_2)_5\text{CH}_3$$

Empirical formula:  $C_{16}H_{34}N_2O_2$

2. Chemical name: 1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline (CHR5)

Chemical Abstract Service Registry No.: None

**Structural formula:**



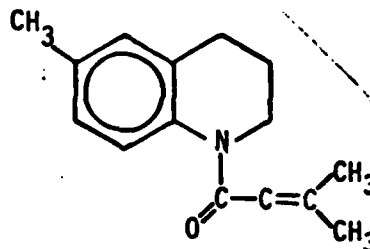
Empirical formula:  $C_{15}H_{19}NO$



3. Chemical Name: 1,2,3,4-Tetrahydro-6-Methyl-1-(3-Methyl-1-Oxo-2-Butenyl) Quinoline (CHR6)

Chemical Abstract Service Registry No.: None

Structural formula:



Empirical formula:  $C_{15}H_{19}NO$

Appendix A provides additional chemical data.

#### Animal Data

Animal data appear in Appendix B.

#### Environmental Conditions

Environmental conditions are stated in Appendix C.

#### Dosing

The nine rabbits were weighed, randomized, and examined. Fluorescein dye and ultraviolet light was used to determine any pre-existing corneal damage 24 hours before the application of the test chemical. No eye lesions were observed.

Three rabbits were assigned to a group for each test chemical. Each rabbit was secured in a restraint cage and the test substance was placed in the right eye of each animal by gently pulling the lower lid away from the eyeball (conjunctival cul-de-sac) to form a cup into which 0.1 ml of liquid (or solid, as in the case of CHR5) was placed. The eyelids were then held together gently to prevent immediate loss of the chemical. The other eye, remaining untreated, served as the negative control. The animals were observed at 1 hour, 24 hours,

48 hours, 72 hours, 4 days, 7 days, 10 days, and 14 days after exposure. The scale for scoring appears in Table 1.

TABLE 1  
GRADES FOR OCULAR LESIONS

## CORNEA

Opacity: degree of density (area dense taken for reading) No ulceration or opacity.....	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster, details of iris clearly visible).....	1*
Easily discernible translucent areas, details of iris slightly obscured.....	2
Mareous areas, no details of iris visible, size of pupil barely discernible.....	3
Opaque cornea, iris not discernible through opacity.....	4

## IRIS

Normal.....	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperemia or injection, any of these or any combination thereof, iris still reacting to light (sluggish reaction is positive).....	1*
No reaction to light, hemorrhage, gross destruction (any or all of these).....	2

## CONJUNCTIVAE

Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)	
Blood vessels normal.....	0
Some blood vessels definitely hyperemic (injected).....	1
Diffuse, crimson color, individual vessels not easily discernible....	2*
Diffuse beefy red.....	3
Chemosis: lids and/or nictitating membranes	
No swelling.....	0
Any swelling above normal (including nictitating membranes).....	1
Obvious swelling with partial eversion of lids.....	2*
Swelling with lids about half-closed.....	3
Swelling with lids more than half-closed.....	4

\*Indicates minimum level for a positive response (3)

### Rationale for Using the Test

The use of animal eyes as test subjects for both pharmacological and toxicological examination has been a well-established procedure for a number of years (1). according to earlier technics, six to nine albino rabbits per test chemical were used (2). The U.S. Interagency Regulatory Liaison Group suggests that a trial test be conducted on three rabbits per test substance, and if the substance produces a positive reaction (corrosion, severe irritation) or a negative reaction (slight or no irritation), then no further testing is necessary (3). If equivocal results occur, three more rabbits are tested.

Before and after chemical exposure, ocular reactions are scored with the unaided eye (4). Observations and scoring are conducted according to Table 1 (3). The eyes of all rabbits are further examined after applying fluorescein stain. After flushing out the excess fluorescein with physiological saline, injured areas of the cornea appear green under ultraviolet light.

Any additional observations, such as pannus, phlyctena, rupture of the globe, and vascularization of the cornea, are reported. The grades of ocular reaction are recorded at each examination.

Method of Analysis: Ulceration of the cornea (other than fine stippling), opacity of the cornea (beyond just slight dulling), inflammation of the iris (other than a slight deepening of the rugae or light hyperemia of circumcorneal blood vessels), or obvious swelling of the eyelids were considered to be signs of positive eye irritation (4).

### Duration of Study

A list of historical events appears in Appendix D.

### Deviations From Original Protocol

None.

## RESULTS

Tabular scoring data appear in Appendix E.

### CHR4

All three of the rabbits receiving 0.1 ml of CHR4 showed signs of corneal opacity at a level of severity of 2 (easily discernible translucent areas with details of the iris slightly obscured). For animal 82F141, this level of opacity persisted throughout the study, and by day 14 vascularization of the cornea and hair loss around the eye were observed. In animals 82F139 and 82F143, level 2 opacity persisted to day 4 after dosing, and then decreased to a score of 1. Slight vascularization of the cornea was observed in animal 82F139 by day 10 (Table 1).

Only one rabbit in this group, 82F141, showed signs of inflammation of the iris. This observation, recorded at 48 hours after dosing, showed heavy hyperemia of the circumcorneal blood vessels. No other rabbit in this group showed signs of serious iridial inflammation during the study (Table 2).

Serious conjunctival reactions were seen in animals dosed with CHR4. Level 2 conjunctival redness was seen in rabbit 82F143 through day 4, while 82F141 and 82F139 remained at level 1 (Table 3). In terms of conjunctival chemosis, all rabbits showed level 2 reactions at some point in the study, with 82F143 again showing the most severe reaction. The level of chemosis seen in the bulbar and palpebral conjunctiva for this animal resulted in a score of 4 (swelling with eyelids more than half-closed) at the 48-hour observation (Table 4).

### CHR5

Of the three animals tested in this group, none showed any signs of corneal opacity or iritis (Tables 5 and 6). Slight redness (score of 1) was seen in rabbits 82F145 and 82F138 at the 24-hour and 48-hour observation. This same degree of redness was seen in rabbit 82F150 at the 24, 48, and 72-hour observation (Table 7). Slight chemosis was observed in the eyes of animals 82F145 and 82F150 at the 24-hour observation, and in the eye of animal 82F138 at the 24-hour and 48-hour observation (Table 8).

### CHR6

Of the three animals tested in this group, none showed signs of corneal opacity or iritis (Tables 9 and 10). Slight redness was seen in the eye of rabbit 82F142 up to the 72-hour observation, in 82F147 up to the 48-hour observation and in 82F146 up to the 24-hour observation (Table 11). Only rabbit 82F142 showed signs of conjunctival chemosis, and scores of 1 were recorded for this animal at the 24 and 48-hour observation periods (Table 12).

## DISCUSSION

In this study, a positive reaction is defined as an animal exhibiting one or more of the following signs (above a given level of severity): ulceration of the cornea, opacity of the cornea, inflammation of the iris, and an obvious swelling of the conjunctiva (accompanied by redness).

Based on these criteria, only CHR4 qualifies as a positive ocular irritant. CHR4 applied to the eyes of three rabbits resulted in readily noticeable corneal opacity, conjunctival redness, and severe conjunctival chemosis. In addition to these signs, other serious symptoms such as vascularization of cornea, heavy hyperemia of circumcorneal blood vessels, and hair loss around the eye were noted. Irritation in the form of conjunctival redness and chemosis was noted in early observations of animals doses with CHR5 and CHR6, but the level of severity did not meet the criteria set forth for positive ocular irritants.

## CONCLUSION

The test compound methyl N,N'-dihexylethylenediamine monocarbamate (CHR4) was judged a positive ocular irritant according to the Primary Eye Irritation test. CHR5 and CHR6 were slightly irritating to ocular tissues, but are classified as a negative ocular irritants.

## RECOMMENDATION

At its present concentration CHR4 should not be considered a safe chemical to use around the face and eyes. Concentrations that are encountered in normal use may demonstrate reduced risk and should be tested. CHR5 and CHR6 should be cleared in the pure state as low risk chemicals, and should undergo further toxicologic testing.

#### REFERENCES

1. Hazelton LW. Relation of surface active properties to irritation of the rabbit eye. Toilet Goods Assoc 1952; 17:5-9.
2. Draize JJ, Kelly EA. Surface active agents and the eye. Drug Cosmetic Ind 1952; 71:36-37.
3. U.S. Interagency Regulatory Liaison Group. Acute eye irritation testing. 1981.
4. Editorial Committee of Food and Drug Officials of the United States. Appraisal of the safety of chemicals in foods, drugs, and cosmetics. 1959. Association of Food and Drug Officials of the U.S.

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Kellner--10



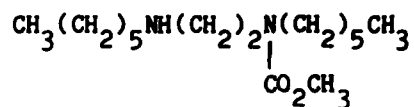
## CHEMICAL DATA

CHR4

1. Chemical name: Methyl N,N'-Dihexylethylene-Diaminemonocarbomate

Chemical Abstract Service Registry No.: None

Structural formula:



Empirical formula:  $\text{C}_{16}\text{H}_{34}\text{N}_2\text{O}_2$

Molecular weight: 286.461

pH: N/A nonaqueous

Physical state: Liquid

Boiling point:  $146^\circ\text{C}/286.461$

Compound density: 0.87 g/ml

Compound refractory index: Unknown

Stability: Stable at room temperature

Names of contaminants and percentages: Unknown

Manufacturer: SRI International  
333 Ravenswood Avenue  
Menlo Park, CA 94025

Manufacturer Lot No: 3K38075

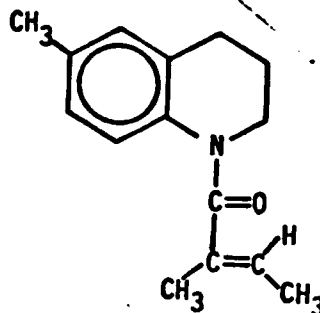
APPENDIX A

CHR5

2. Chemical name: (E) 1,2,3,4-tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl)Quinoline

Chemical Abstracts Service Registry No.: None

Structural formula:



Empirical formula:  $C_{15}H_{19}NO$

Molecular weight: 229

pH: N/A nonaqueous

Physical state: Liquid

Boiling point: Unknown

Compound density: Unknown

Compound refractory index: Unknown

Stability: Unknown

Names of contaminants and percentages: Unknown

Manufacturer: SRI International  
333 Ravenswood Avenue  
Menlo Park, CA 94025

APPENDIX A (Cont)

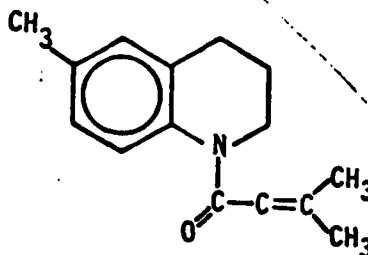
Manufacturer Lot No.: 4214H31

CHR6

3. Chemical Name: 1,2,3,4-Tetrahydro-6-Methyl-1-(3-Methyl-1-Oxo-2-Butenyl)Quinoline

Chemical Abstracts Service Registry No.: None

Molecular structure:



Empirical formula: C<sub>15</sub>H<sub>19</sub>NO

Molecular weight: 229

pH: N/A nonaqueous

Physical state: Liquid

Boiling range: Unknown

Compound density: Unknown

Compound refractory index: Unknown

Stability: Unknown

Names of contaminants and percentages: Unknown

Manufacturer: SRI International  
333 Ravenswood Avenue  
Menlo Park, CA 94025

Manufacturer Lot No.: 3905H3

APPENDIX A (Concluded)

Kellner--14

ANIMAL DATA

Species: Rabbit

Strain: New Zealand White (albino)

Source: Elkhorn Rabbitry  
5265 Starr Way  
Watsonville, CA 95076

Sex: Male

Age: Young adults

Method of randomization: RANDOM Program on eclipse C330 computer (SOP  
OP-ISG-21).

Animals in dose group: 3 (3 groups)

Condition of animals at start of study: Normal

Body weight range: 2405-2977 g;  $\bar{x}$  = 2669; s = 197

Identification procedures: Ear tattoo (SOP-OP-ARG-1)

Pretest conditioning:

1. Quarantine from 10 February-24 February 1983
2. Animal eyes were examined 24 hours before dosing using fluorescein dye and ultraviolet light.

Justification: Rabbits are a proven sensitive animal model for this test

Kellner--16

ENVIRONMENTAL CONDITIONS

Caging: Number/cage = 1; type of cage = stainless steel, wire mesh bottom, battery type, no bedding, automatic flush.

Diet: Purina Certified Rabbit Chow No. 5322, approximately 110 g/day  
Lot No. JUL09821C and JAN28822A

Water: Central line to cage battery with automatic lick dispensers

Temperature:  $76 \pm 3$  F ( $24 \pm 1$  C)

Humidity:  $42 \pm 5\%$

Photoperiod: 0530-2000 hours per day (light 14-1/2 hours)

Kellner--18



## HISTORICAL LISTING OF STUDY EVENTS

<u>Date</u>	<u>Event</u>
9 Sep 82	Rabbits arrived at LAIR. They were weighed, tattooed (SOP-ARG-1), or labelled, checked for illness, and quarantined by Animal Resources Group for 2-3 weeks.
27 Sep 82	Rabbits were removed from quarantine, separated into test groups, and weighed.
28 Sep 82	Rabbits were dosed according to test chemical group and weighed. 1-hour after dosing the eyes were observed and scored.
29 Sep 82	24 hours after dosing the eyes were observed and scored.
30 Sep 82	48 hours after dosing the eyes were observed and scored.
1 Oct 82	Animals were weighed. 72 hours after dosing the eyes were observed and scored.
2 Oct 82	4 days after dosing the eyes were observed and scored.
5 Oct 82	7 days after dosing the eyes were observed and scored.
3-12 Oct 82	Rabbits were observed daily if scores were not performed.
8 Oct 82	Animals were weighed. 10 days after dosing the eyes were observed and scored.
12 Oct 82	Animals were weighed. 14 days after dosing the eyes were observed and scored.
12 Oct 82	Animals were taken off study because recovery or irreversibility was indicated.

Kellner--20

TABULAR SCORING DATA  
ON ACUTE EYE IRRITATION SUMMARY FORMS

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Kellner--22

Table 1  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Cornea

GLP Study No. 82027 Chemical Name CHR4  
Principal Investigator Hanes/Kellner Physical State Liquid  
Date Started 28Sep82 Amount Applied 0.1 ml

Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F141	2	2	2	2	2	2	1	2
82F139	2	2	2	2	2	1	1	1
82F143	1	2	2	2	2	1	1	1

Table 2  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Iris

GLP Study No. 82027 Chemical Name CHR4

Principal Investigator Hanes/Kellner Physical State Liquid

Date Started 28Sep82 Amount Applied 0.1 ml

Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F141	0	0	1	0	0	0	0	0
82F139	0	0	0	0	0	0	0	0
82F143	0	0	0	0	0	0	0	0

Table 3  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Conjunctiva - redness

GLP Study No. 82027 Chemical Name CHR4  
Principal Investigator Hanes/Kellner Physical State Liquid  
Date Started 28Sep82 Amount Applied 0.1 ml

## Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F141	1	1	1	1	1	0	0	1
82F139	1	1	1	1	1	0	0	0
82F143	1	2	2	2	2	1	0	0

Table 4  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Conjunctiva - chemosis

GLP Study No. 82027 Chemical Name CHR4  
Principal Investigator Hanes/Kellner Physical State Liquid  
Date Started 28Sep82 Amount Applied 0.1 ml

Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F141	2	2	2	2	2	1	1	0
82F139	3	2	1	1	1	1	1	0
82F143	3	3	4	3	2	1	0	0



Table 5  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Cornea

GLP Study No. 82027 Chemical Name CHR5  
Principal Investigator Hanes/Kellner Physical State Solid  
Date Started 28Sep82 Amount Applied 0.1 ml (less than 0.1 g)

Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F145	0	0	0	0	0	0	0	0
82F138	0	0	0	0	0	0	0	0
82F150	0	0	0	0	0	0	0	0

Table 6  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Iris

GLP Study No. 82027

Chemical Name CHR5

Principal Investigator Hanes/Kellner

Physical State Solid

Date Started 28Sep82

Amount Applied 0.1 ml (less than 0.1 g)

Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F145	0	0	0	0	0	0	0	0
82F138	0	0	0	0	0	0	0	0
82F150	0	0	0	0	0	0	0	0

Table 7

## Acute Eye Irritation Summary

## Rabbits

Area Summarized Conjunctiva - rednessGLP Study No. 82027Chemical Name CHR5Principal Investigator Hanes/KellnerPhysical State SolidDate Started 28Sep82Amount Applied 0.1 ml (less than 0.1 g)

## Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F145	0	1	1	0	0	0	0	0
82F138	0	1	1	0	0	0	0	0
82F150	0	1	1	1	0	0	0	0

Table 8  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Conjunctiva - chemosis

GLP Study No. 82027 Chemical Name CHR5  
Principal Investigator Hanes/Kellner Physical State Solid  
Date Started 28Sep82 Amount Applied 0.1 ml (less than 0.1 g)

Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F145	0	1	0	0	0	0	0	0
82F138	0	1	1	0	0	0	0	0
82F150	0	1	0	0	0	0	0	0

Table 9  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Cornea

GLP Study No. 82027 Chemical Name CHR6  
Principal Investigator Hanes/Kellner Physical State liquid  
Date Started 28Sep82 Amount Applied 0.1 ml

Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F142	0	0	0	0	0	0	0	0
82F147	0	0	0	0	0	0	0	0
82F146	0	0	0	0	0	0	0	0

Table 10  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Iris

GLP Study No. 82027 Chemical Name CHR6  
Principal Investigator Hanes/Kellner Physical State liquid  
Date Started 23Sep82 Amount Applied 0.1 ml

## Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F142	0	0	0	0	0	0	0	0
82F147	0	0	0	0	0	0	0	0
82F146	0	0	0	0	0	0	0	0

Table 11  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Conjunctiva - redness

GLP Study No. 82027 Chemical Name CHR6  
Principal Investigator Hanes/Kellner Physical State liquid  
Date Started 23Sep82 Amount Applied 0.1 ml

Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F142	0	1	1	1	0	0	0	0
82F147	0	1	1	0	0	0	0	0
82F146	0	1	0	0	0	0	0	0

Table 12  
Acute Eye Irritation Summary  
Rabbits

Area Summarized Conjunctiva - chemosis

GLP Study No. 82027 Chemical Name CHR6  
Principal Investigator Hanes/Kellner Physical State liquid  
Date Started 23Sep82 Amount Applied 0.1 ml

Score by Animal

Rabbit No.	1 hr	24 hr	48 hr	72 hr	4 d	7 d	10 d	14 d
82F142	0	1	1	0	0	0	0	0
82F147	0	0	0	0	0	0	0	0
82F146	0	0	0	0	0	0	0	0

APPENDIX E (concluded)



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